REMARKS

Claims 49, 63-71, 77-81, 83, 88, 89, 91 and 92 are pending in the present application.

Interview Conducted with Patent Examiner

Applicant's representative appreciates the time and consideration given by the Patent Examiner during a telephonic Interview which was conducted earlier today in order to discuss the various issues arising in connection with the above-identified application. In summary, Applicant's representative emphasized that there are significant structural distinctions between the compounds of the present invention and the compounds disclosed in each of the Ottosen '744 (WO 2001/05744), Revesz '447 (WO2002/764447), and Ottosen '670 (US 6,541,670) references which support the previous rejection under 35 USC 103(a) and previous obviousness-type double patenting rejection. For example, Ottosen '744 requires the presence of an amino group on "Ring C" (the phenyl group bonded to the linking amino group), Revesz '447 requires the absence of any substituents on the center "Ring B", and Ottosen '670 both fails to include the methyl group on Ring A or the R_5/R_6 group on Ring A, based on a comparison against present claim 49. In addition, Applicant has identified significant comparable test data which supports a conclusion that the compounds of the presently claimed invention exhibit advantageously improved inhibition properties with respect to IL-1β and TNF-α, which test data is discussed in more detail below. The Examiner tentatively agreed that upon further reflection there appear to be patentable distinctions between the present claims and the above-noted references. Below are remarks that essentially repeat the various points submitted with the previous Amendment filed June 8, 2010.

Unity of Invention Issues

Applicant respectfully maintains a traversal of the Unity of Invention Requirement for the reasons stated in Response filed May 28, 2008 which reasons are deemed repeated herein.

Issues under 35 USC 103(a)

Claims 49, 63-65, 67, 69-71, 77, 78, 81 and 91 were previously rejected under 35 USC 103(a) as being unpatentable over Ottosen '744 (WO 2001/05744) in view of Revesz '447 (WO 2002/76447). This rejection is traversed based on the following reasons.

As a preliminary matter, it is noted that on the first page of the present specification, Rings "A", "B" and "C" are identified in the structure of the compounds of the present invention, with Ring A being the end phenyl group bonded to the linking carbonyl group, Ring B being the center phenyl group, and Ring C being the other end phenyl group bonded to the linking amino group.

Patentable Distinctions over Ottosen '744 and Revesz '447

Ottosen '744 fails to disclose or suggest any of the compounds of the present invention because the claimed compounds do not include an amino group as a possible R_3 or R_4 substituent in formula I in the present claims. Rather, R_3 and R_4 in the claimed compounds are both fluoro in fixed positions on Ring C. Therefore, significant structural distinctions exist over the compounds of Ottosen '744.

Revesz '447 discloses compounds of formula I wherein R4 in Ring C may be 1-3 halogens, and the middle phenyl ring ("Ring B") is unsubstituted. The Examiner refers to Example 3 on page 14 which shows a structure with fluoro atoms at the para and meta positions on Ring C (with respect to the linking amino group) and an unsubstituted middle Ring B. Revesz '447 fails to disclose or suggest the compounds of formula I of the present claims, wherein Ring B must be substituted. Therefore, significant structural distinctions exist over the compounds of Revesz '447.

Asserting that Ottosen '744 is the closest prior art, the Examiner acknowledges that Ottosen '744 fails to disclose any compounds wherein R3 and R4 are fluoro, with R3 being meta to R4 and para to the linking amino group. The Examiner further acknowledges novelty over Revesz '447 but concludes that since Revesz '447 discloses the above-noted Example 3 compound, "...it would have been obvious to one of ordinary skill in the art..... to synthesize the compound of Ottosen et al. and modify the R3 and R4 groups with the fluorine atoms of Revesz with a reasonable expectation of success."

Applicant respectfully disagrees. First of all, one skilled in the art would not be motivated to replace the amino group on Ring C of the compounds of Ottosen '744 with a fluorine atom, since the amino group on Ring C of Ottosen '744 constitutes an essential part of the structure of the compounds disclosed therein. Secondly, one skilled in the art would find no reasonable basis for a motivation to place a substituent on the middle Ring B of the compounds

of Revesz '447. Essentially, the Examiner is arguing that one skilled in the art would be motivated to make two significant structural changes, one in each of the compound sets of Ottosen '744 and Revesz '447, despite the fact that all compounds in both references do not have these structural features and both references fail to provide any suggestion or hint to make such modifications. Why would one skilled in the art decide to make both of these selective structural changes to the compounds of both Ottosen '744 and Revesz '447? This question remains unanswered apart from an unsupported conclusion that it would have been obvious.

If one skilled in the art studied Revesz '447 and were hypothetically inclined to try replacing an amino group on Ring C of an aminobenzophenone structure, he would learn from US 6,541,670 (Ottosen '670), which concerns aminobenzophenone compounds similar to the present invention, that substitution on Ring C with fluoro would indeed ***not*** provide compounds with an improved TNF-α or IL-1β inhibitory activity compared to the similar compounds without the fluoro atom being present. In this regard, note that compounds 102, 116, 130, 131 in Ottosen '670 are identical except that compounds 116, 130 and 131 have a fluoro atom in the 4, 5 and 3 position, respectively, whereas compound 102 has a hydrogen atom in this position. The skilled person comparing these compounds would find that compounds 116 and 130 indeed show a difference in the pharmacological properties compared to compound 102, but in a non-beneficial way. In fact the TNF-α or IL-1β inhibitory activity for 116 and 130 are considerably decreased compared to compound 106 and at the same level for compounds 131 and 102. See IC_{50}-values (nM) extracted from table 1 in Ottosen '670 below:

Compound:	IL-1β	TNF-α
102	13	4.0
116	2	7.9
130	40	6.3
131	13	4.0

For comparison, the compounds of the present invention show IL-1β and TNF-α inhibition concentration-values (IC_{50}) of <13 nM and <4 respectively as evidenced by the results in Table 1 in the present application as filed.

Therefore, a skilled person having reviewed Revesz '447 and Ottosen '670 would indeed not be able to predict that replacing the amino group in Ring C in a benzoaminophenone compound similar to the compounds according to the present invention would yield compounds with a considerably improved inhibitory TNF-α or IL-1β activity. Further, one skilled in the art would not have any reasonable basis to be inclined to replace the amino group in Ring C with two fluoro groups, as the amino group constitutes an essential part of the structure of the compounds disclosed in Ottosen '744. Consequently, significant patentable distinctions exist over both Ottosen '744 and Revesz '447, whether taken separately or improperly combined.

Furthermore, Ottosen '744 fails to disclose or suggest the substitution pattern of Ring A in the claimed compounds, i.e. 2-methyl as R_1 and R_5 and R_6 with the substituents stated in claim 49.

In vitro inhibition data of the compounds of Ottosen '744 were shown during the international phase examination of the corresponding PCT application. Please find below an extract from the response to the Written Opinion (Ottosen '744 being referred to as D1). The table shows inhibition of cytokines production *in vitro* by compounds of Ottosen '744 (IC_{50}, nM or magnitude median inhibition concentration) relative to reference compounds a–f of the present invention (see also pages 43-47 of the published PCT application WO 2005/009940):

Document	Compound	IL-1β	TNF-α
D1	D1 / 112	= 16	> 9 (D1 /136)
	D1 / 117	> 16 (D1 /112)	> 9 (D1 /136)
	D1 / 118	> 16 (D1 /112)	> 9 (D1 /136)
	D1 / 135	> 16 (D1 /112)	> 9 (D1 /136)
	D1 / 136	> 16 (D1 /112)	= 9 (D1 /136)
	D1 / 138	> 16 (D1 /112)	> 9 (D1 /136)
	D1 / 139	> 16 (D1 /112)	> 9 (D1 /136)
	D1 / 140	> 16 (D1 /112)	> 9 (D1 /136)
	D1 / 142	> 16 (D1 /112)	> 9 (D1 /136)

As it can be seen from the above table, compounds disclosed in Ottosen '744 are quantitatively less active in comparison to the reference compounds a (D9), b (D3), c (D4), d (D5), e (D2) and f (D6). Since the compounds of the present invention show IC_{50} values for IL-1β in the range 0.4-8.9 and for TNF-α in the range 0.2-3.2, it is clear that the compounds of the present application encompassed within the definition of claim 1 are substantially improved over the compounds disclosed in Ottosen '744.

Revesz '447 discloses compounds having a distinctly different substitution pattern compared to the compounds of the present invention, containing inter alia no substituents on Ring B. Furthermore Revesz '447 does not reveal compounds wherein R_1 is methyl.

Further in addition to the above, one skilled in the art, with knowledge of Revesz '447 and Ottosen '670, would indeed not be able to predict that replacing a hydrogen atom in Ring C in a benzoaminophenone analogue of compounds according to the present invention and adding a substituent at the 3 position of middle Ring B, would yield compounds with a considerably improved inhibitory TNF-α or IL-1β activity compared to the benzoaminophenone analogues described in the prior art. Revesz '447 does not disclose any *in vitro* inhibition data, but reports that agents of the invention typically inhibit *in vivo* TNF-α production from about 50% up to about 90% or more when administered at 30 mg/kg p.o. (page 42). As can be seen from Table 3 of the present application, compounds of the present invention inhibit *in vivo* TNF-α production from about 44% to 99% when administered at just 1 mg/kg p.o. Thus, the dosing of compounds of the present invention is 30 times less in comparison to the dosing of the compounds of Revesz '447 in an otherwise comparable assay. Compounds of the present invention therefore show unexpected, advantageously improved biological activity *in vivo* with respect to inhibition of LPS induced TNF-α production in mice compared to the compounds of Revesz '447, with no recognition of this improvement mentioned in either the Revesz '447 or Ottosen '744 references.

In conclusion, it is the position of the Examiner that it would have been obvious to replace the optionally substituted amino group on Ring C of the compounds of Ottosen '744 with two fluoro groups (at the meta and para positions), or to place a substituent on the middle Ring B of Revesz '447 even though none exists in any of the disclosed compounds, or to selectively combine structural features of both sets of compounds from each reference, in an attempt to obtain the presently claimed compounds. However, the present record is not only devoid of any

reasonable basis to suggest any improvements with such modifications, but the most relevant evidence noted above suggests that such modifications would provide inferior results. For example, as noted above, the dosing of compounds of the present invention is 30 times less in comparison to the dosing of the compounds of Revesz '447 in an otherwise comparable assay. Compounds of the present invention show therefore surprisingly an improved biological activity in vivo with respect to inhibition of LPS induced TNF-α production in mice compared to the compounds of Revesz '447. These results are clearly unexpected as it is difficult to understand the Examiner's belief that "the results are [not] strong enough to overturn the strong *prima facie* case of obviousness that has been set forth" (page 3 of the Office Action). In this regard, note that there must be some evidence of at least a reasonable expectation of success to support such modifications. *KSR International Co. v. Teleflex Inc.*, 85 USPQ2d 1385, 1395 (US Sup. Ct. 2007). The only basis for selectively combining Ottosen '744 with Revesz '447 is improper "hindsight reconstruction" which ignores the fact that both references disclose compound structures inconsistent with the proposed modifications and suggesting to one skilled in the art that such modifications would render the compounds unsatisfactory for their intended purpose. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Consequently, the above rejection fails to be supported and must be withdrawn.

Double Patenting Rejection

Claims 49, 50 63-71, 77-81 and 91 were previously rejected on the ground of obviousness-type double patenting as being upatentable over claim 1 of Ottosen '670 (US 6,541,670) in view of Revesz '447 (WO 2002/76447). This rejection is traversed based on the following reasons.

The compounds encompassed by the present claims are not only distinct from the claims of Ottosen '670 with respect to the R_5/R_6 substituents and the fixed 2,4-difluoro-phenyl ring, they also show considerably improved inhibitory activity towards TNF-α or IL-1β as compared to the compounds claimed in Ottosen '670. Note the comparative data discussed above and Table 1 in the present application as filed. From this comparison it is clear that the compounds of Ottosen '670 having a fluoro substituent on Ring C show considerably poorer TNF-α or IL-1β activity than the unsubstituted equivalents. There is therefore no incentive for a person skilled in

the art to modify the compounds of Ottosen '670 with the fluoro atoms of Revesz '447 with any reasonable expectation of success. Ottosen '670 has been improperly combined with Revesz '447 based on improper hindsight. Consequently, the above double patenting rejection should be withdrawn.

It is submitted for the reasons above that the present claims define patentable subject matter such that this application should now be placed in condition for allowance.

If any questions arise in the above matters, please contact Applicant's representative, Andrew D. Meikle (Reg. No. 32,868), in the Washington Metropolitan Area at the phone number listed below.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

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